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Effects of Oral Cimetidine and Ranitidine on Gastric pH and Residual Volume in Children

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The effect of orally administered cimetidine 7.5 mg/kg (group 1), ranitidine 1.5 mg/kg (group 2), ranitidine 2.0 mg/kg (group 3), or a placebo (group 4) on gastric *p*H and gastric residual volume of 60 healthy children 2–6 yr of age admitted for elective surgery was evaluated. Both cimetidine and ranitidine administered 1–2 h prior to induction of anesthesia effectively increased the gastric *p*H: 5.47 ± 1.85 ml/kg (group 1), 4.92 ± 2.1 ml/kg (group 2), 5.30 ± 1.82 ml/kg (group 3) compared with 1.75 ± 0.58 ml/kg (group 4) ($P < 0.001$). A single dose of ranitidine 1.5 mg/kg was as effective as ranitidine 2.0 mg/kg and cimetidine 7.5 mg/kg. Neither drug decreased the gastric residual volume: 0.32 ± 0.33 ml/kg (group 1), 0.31 ± 0.06 ml/kg (group 2), 0.23 ± 0.05 ml/kg (group 3), and 0.33 ± 0.05 ml/kg (group 4). The combination of a volume > 0.4 ml/kg and a *p*H < 2.5 was found in 33% (five of 15) of patients in the placebo group (group 4). In contrast, there were no patients with this combination in groups 1, 2, or 3 ($P < 0.001$). (Key words: Anesthesia: pediatric. Complications: aspiration pneumonitis. Histamine: cimetidine; ranitidine.)

CIMETIDINE OR RANITIDINE administered to adults preoperatively have been reported to increase gastric *p*H and decrease gastric residual volume compared with patients to whom no histamine blocking drugs had been given.[1,2] In children a single oral dose of cimetidine 7.5 mg/kg resulted in a gastric fluid *p*H greater than 2.5 in 95% of patients, with decreased volume of gastric contents.[3,4] Ranitidine 2.0–3.5 mg/kg po 1–4 h prior to anesthesia increased the gastric *p*H without affecting gastric volume.[5] Pharmacokinetic and pharmacodynamic data for ranitidine, however, suggest that an oral dose of ranitidine 1.25 to 1.9 mg/kg decreases gastric acid secretion by 90%.[6] In this study we compared the effects of ranitidine po (1.5 and 2.0 mg/kg) with that of cimetidine po (7.5 mg/kg) on gastric *p*H and gastric residual volume of children treated prior to induction of anesthesia.

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Methods

The protocol was approved by the hospital ethics committee; informed written consent was obtained for all patients. We studied 60 ASA physical status 1 and 2 children 2–6 yr of age scheduled for elective anesthesia and operation. They had no history of active gastrointestinal disease and were receiving no medication. Each patient had been fasting for 8 h or longer and received no preanesthetic medication. Children were randomly divided into four treatment groups. One to two hours prior to induction of anesthesia, they received orally cimetidine 7.5 mg/kg (group 1), ranitidine 1.5 mg/kg (group 2), ranitidine 2.0 mg/kg (group 3), or a placebo (group 4). The precise time of treatment administration, induction of anesthesia, and aspiration of gastric content was recorded. An oral solution of cimetidine (60 mg/ml) was utilized. Because there was no oral solution of ranitidine available, an iv solution (25 mg/ml) was used. Orange flavored syrup and dextrose 10% were used to make ranitidine and cimetidine solutions more palatable. The total volume administered to each patient was 5 ml. The placebo was made of orange syrup and dextrose 10% only. All solutions were prepared a few minutes prior to administration by one author (B.G.) to ensure the stability of the solution. The *p*H of the different preparations were 5.7, 6.8, 6.8, and 4.5 for groups 1, 2, 3, and 4, respectively.

Anesthesia was induced *via* mask with nitrous oxide 65%, oxygen 33%, and halothane 2%. Following insertion of an iv catheter, atropine 0.01 mg/kg was administered by a bolus injection. When the level of anesthesia was deemed adequate, the trachea was intubated without the use of a muscle relaxant. Gastric contents were aspirated using a number 12 Salem Sump® tube (Argyle) inserted orally by an anesthesiologist who was unaware of the drug being studied. The position of the orogastric tube was confirmed by observation of an indentation produced by the gastric tube on the epigastrium, by auscultation over the epigastrium while air was injected rapidly into the tube and by aspiration of gastric contents. The volume of gastric content aspirated was measured with a syringe. The *p*H was measured in triplicate after centrifugation with a Fisher *p*H meter (#620) using a glass electrode 13-639-94 microprobe (Allied Fisher Scientific, Orangeburg, New York), which has a precision of 0.01 *p*H unit over

TABLE 1. General Patient Data

Treatment	N	Sex (F/M)	Age (yr)	Weight (kg)	TI (min)	TA (min)	IA (min)
Cimetidine 7.5 mg/kg (group 1)	15	3/12	4.1 ± 1.6	16.8 ± 4.6	78 ± 16	86 ± 14	9 ± 2
Ranitidine 1.5 mg/kg (group 2)	15	5/10	5.1 ± 1.6	19.6 ± 5.5	82 ± 14	92 ± 14	10 ± 3
Ranitidine 2.0 mg/kg (group 3)	15	7/8	4.3 ± 1.5	17.9 ± 4.5	80 ± 14	88 ± 14	8 ± 2
Placebo (group 4)	15	5/10	4.1 ± 1.7	17.9 ± 5.4	84 ± 17	92 ± 16	9 ± 3

the entire *p*H range. The electrode was calibrated using standard buffers of *p*H 4, 7, and 10. Recalibration was performed after no more than nine measurements.

If no gastric fluid could be aspirated, the patient was considered to have a gastric residual volume of zero. Data from such patients were included for comparison of mean gastric volume and the possible combination of a *p*H lower than 2.5 and a volume greater than 0.4 ml/kg but were excluded for comparison of mean *p*H. The mean *p*H and volume of gastric contents were compared by a multivariate analysis with mean age, height, weight, time from treatment to induction (TI), from treatment to gastric aspiration (TA), and time from induction of anesthesia to gastric aspiration (IA) as covariates. Each of these factors was assessed by variance-covariance analysis. Sex distribution and the possible combination of a *p*H less than 2.5 and a volume greater than 0.4 ml/kg were analyzed by the chi-square test using the Yates' correction. Statistical significance was assumed if $P < 0.05$.

Results

There were no statistical differences between the groups for mean age, sex, height, weight, TI, TA, and IA (table 1). The gastric residual volumes (ml/kg) were comparable in all patients (table 2). In six patients the volumes of gastric contents were insufficient to measure the *p*H: three patients in group 1, one patient in group 2, one patient in group 3, and one patient in group 4. The control group (group 4) had a significantly lower mean *p*H than any of the other three groups ($P < 0.001$), which in turn were not statistically different from one another (table 2). In groups 1, 2, and 3 there were no patients with the combination of both a *p*H lower than 2.5 and a volume greater than 0.4 ml/kg (fig. 1). However, this combination was found in 33% (five of 15) of the control group patients (group 4) ($P < 0.001$).

Discussion

The critical *p*H of gastric contents that has the potential to induce a severe pneumonitis is a function of the volume aspirated. In rats the tracheal injection of a volume of 0.4 ml/kg or less and a *p*H of 2.5 or greater of an hydrochloric acid solution buffered with sodium hydroxide has been shown to induce no late mortality.[7,8] Although one cannot extrapolate animal data to humans, this nonlethal *p*H-volume combination is absent in 10–76% of pediatric patients undergoing elective surgery, *i.e.*, 10–76% of patients may be at potential risk.[3,9,10,11] In our study 33% (five of 15) of patients in the control group had both a gastric fluid *p*H < 2.5 and a volume > 0.4 ml/kg. Cimetidine and ranitidine were equally effective in increasing gastric *p*H, and no patient in any treatment group had both a *p*H less than 2.5 and a volume greater than 0.4 ml/kg.

Inconsistent results have been published on the effects of cimetidine and ranitidine on gastric residual volume. In adults studies report either a decrease or no effect on

TABLE 2. Volume and *p*H of Gastric Aspirate

Treatment	N	Volume (ml/kg)	N	*p*H
Cimetidine 7.5 mg/kg (group 1)	15	0.27 ± 0.32 (0–1.12)	12	5.47 ± 1.82 (1.8–7.2)
Ranitidine 1.5 mg/kg (group 2)	15	0.29 ± 0.21 (0–0.86)	14	4.92 ± 2.05 (1.5–7.2)
Ranitidine 2.0 mg/kg (group 3)	15	0.22 ± 0.19 (0–0.79)	14	5.29 ± 1.82 (2.0–7.3)
Placebo (group 4)	15	0.31 ± 0.19 (0–0.69)	14	1.75 ± 0.58* (1.3–3.6)

Values are mean ± SD; ranges are in parentheses. If no gastric fluid could be aspirated, the patient was considered to have a gastric residual volume of zero. Data from such patients were included for comparison of mean gastric residual volume but were excluded for comparison of mean *p*H.

* $P < 0.001$ *versus* groups 1, 2, and 3.

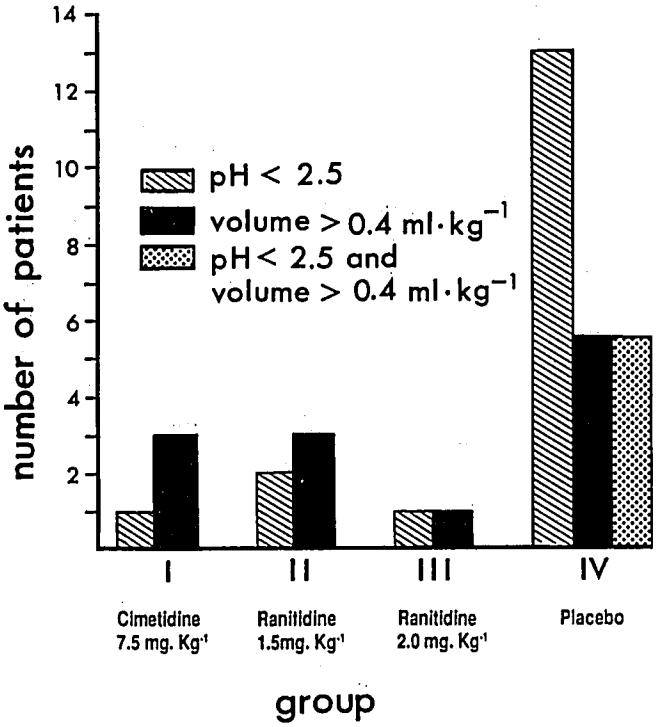

FIG. 1. Number of patients having either a pH < 2.5, a volume > 0.4 ml/kg, or both. Group 4 was statistically different from groups 1, 2, and 3 for the gastric pH and for the combination of both factors ($P < 0.001$).

gastric residual volume with either cimetidine or ranitidine.[1,2] In children cimetidine reportedly decreased the gastric residual volume while ranitidine had no effect.[3-5] These conflicting results might be explained by several factors. The shorter time interval from treatment to aspiration in our study (1–2 h) compared with 1–4 h might have been insufficient to observe the effect on gastric residual volume.[3] Although the volume aspirated through a Salem tube closely approximates the volume obtained by the dilution method, it still may not yield the exact volume of fluid in the stomach.[12] The addition of glucose might have increased the volume of gastric secretions.[13] The fact that the gastric residual volume of our control group (0.33 ± 0.05 ml/kg) is less than that reported in another study in children who received no placebo (0.53 ± 0.1 ml/kg) does not support this possibility.[3] Additionally, atropine might have reduced the gastric volume, although previous reports have shown that atropine has no effect on gastric volume in children.[14]

Of the three different methods of prophylaxis against aspiration of gastric contents used in this study, ranitidine 1.5 mg/kg seems, for several reasons, the most logical choice. First, in contrast to cimetidine, ranitidine does not interfere with hepatic metabolism of morphine, diazepam, theophylline, phenytoin, and other medications.[15] Second, the duration of action of ranitidine is longer than that of cimetidine.[16] Third, ranitidine might also decrease the risk of passive regurgitation by increasing the tone of the inferior esophageal sphincter.[15] However, ranitidine is more expensive than cimetidine and an oral suspension is not yet available.

In summary, both cimetidine and ranitidine, given orally 1–2 h prior to induction of anesthesia, increase gastric pH in children. A single dose of ranitidine (1.5 mg/kg) is as effective as cimetidine (7.5 mg/kg). In this study, neither agent reduced gastric residual volume.

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